Identification of a Novel DHCR7 Mutation in a Korean Patient With Smith-Lemli-Opitz Syndrome

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Clinical Report

A 14-month-old girl was referred to our institution because of developmental delay. She was born spontaneously and uneventfully at a gestational age of 41 weeks and had a birth weight of 2.3 kg (<10th percentile for birth weights in Koreans). No abnormal fetal movement or teratogenic exposures during pregnancy were reported. The parents were not consanguineous. After birth, the patient developed growth failure and experienced difficult feeding. Her motor development was delayed; she was able to control head movements by 7 months of age and sat alone by 14 months of age. During the 2-year follow-up, the delay in her motor and speech development persisted; she walked with assistance at 3 years of age and verbalized “mama” and “papa” at 2 years, 6 months of age. Because she experienced recurrent otitis media and chronic sinusitis, ventricular tubes were inserted in both ears.

The height of the patient was 71.5 cm (<3rd percentile), body weight was 6.9 kg (<3rd percentile), and head circumference was 41 cm (<3rd percentile). She had a cleft palate, bilateral eyelid ptosis, a short nasal root, and bilateral syndactyly of the second and third toes (Fig. 1).

Smith-Lemli-Opitz syndrome is a unique malformation syndrome characterized by a defect in cholesterol biosynthesis, which is very rare among populations in Middle and East Asia. The authors identified compound heterozygous mutations ([p.Arg352Trp] + [p.Lys376ArgfsX37]) in a Korean girl with clinical and laboratory features typical of Smith-Lemli-Opitz syndrome. The Lys376ArgfsX37 mutation is a novel mutation, and to the best of the authors' knowledge, this is the first report of a clinically and genetically confirmed case of Smith-Lemli-Opitz syndrome in Korea.

Keywords: Smith-Lemli-Opitz syndrome; DHCR7 gene

Smith-Lemli-Opitz syndrome is an autosomal recessive disorder of cholesterol biosynthesis associated with multiple congenital anomalies, including characteristic facial dysmorphism, cleft palate, syndactyly of the second and third toes, and variable combinations of other anomalies. Smith-Lemli-Opitz syndrome occurs at a relatively high frequency in Caucasians (1 in 20 000 to 30 000 live births). Although the biochemical and genetic defects of this unique syndrome have been described, there are very few reports of Smith-Lemli-Opitz syndrome in the Middle and East Asian population. To date, more than 100 different mutations of the causative gene (DHCR7) have been identified in Smith-Lemli-Opitz syndrome patients. In this report, we describe a 4-year-old girl with a phenotype characteristic of Smith-Lemli-Opitz syndrome who has compound heterozygote mutations of the DHCR7 gene, one allelic mutation of which (1127-1128delA) is novel. This is the first diagnosis of Smith-Lemli-Opitz syndrome in a Korean to be substantiated by biochemical and genetic assay.

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transaminase level, which then spontaneously reverted to normal levels after a few weeks. Fasting plasma cholesterol levels ranged from 47 to 63 mg/dL, and her 7-dehydrocholesterol level was as high as 176 µg/dL.

**Mutational Analysis**

Blood samples were collected from the patient and her parents after obtaining informed consent. Genomic DNA was isolated from peripheral blood leukocytes using a Wizard genomic DNA purification kit according to the manufacturer's instructions (Promega, Madison, Wisconsin). All coding exons of the DHCR7 gene and their flanking intronic regions were amplified by polymerase chain reaction using the primers designed by the authors (available on request). Cycle sequencing was performed with a BigDye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems, Foster City, California) and an ABI 3100 Genetic Analyzer (Applied Biosystems).

Bidirectional sequencing analysis demonstrated that the patient had a novel deletion mutation (c.1127_1128delA; p.Lys376ArgfsX37) as well as a known missense mutation (c.1054C>T; R352W) in exon 9 of the DHCR7 gene (Fig. 2). Further analysis of the parents revealed that her father and mother were heterozygous carriers of the Lys376ArgfsX37 and Arg352Trp mutations, respectively.

**Discussion**

Smith-Lemli-Opitz syndrome is an autosomal recessive disorder and is a prototypical example of a human malformation/retardation syndrome caused by a defect in cholesterol biosynthesis. The incidence of Smith-Lemli-Opitz syndrome differs between ethnic groups: it is highest in northern Europeans (eg, 1 in 10 000 newborns in middle Bohemia), moderate in Slovakia and Canada (1/20 000 newborns and 1/30 000 newborns, respectively), and low in the United Kingdom (1/60 000 newborns). Tsukahara et al reported that the incidence of Smith-Lemli-Opitz syndrome varied between races and was very low among Africans and Asians, including Japanese. Because the biochemical and genetic abnormalities of Smith-Lemli-Opitz syndrome were elucidated, a few clinically diagnosed cases of Smith-Lemli-Opitz syndrome in Japan and India were reported, and one genetically proven case of Smith-Lemli-Opitz syndrome involving 2 Lebanese families was reported. Recently, Matsumoto et al identified 5 kinds of mutations in 7 Japanese patients with Smith-Lemli-Opitz syndrome and suggested that R352Q is a common founder mutation in this population. One allelic mutation present in our patient, R352W, is similar to the R352Q mutations in that it differs only in the type of amino acid substituted and is 1 of the 8 most common mutations worldwide.

According to the revised scoring system for Smith-Lemli-Opitz syndrome, our patient had a mild phenotype. She was a compound heterozygote for a 1127-1128delA frameshift mutation (null) on 1 allele of the DHCR7 gene and a missense mutation of R352W on another allele of the DHCR7 gene. One of the mutated alleles is a novel mutation, and the other is 1 of the 7 most frequent missense mutations. The mild to moderate typical dysmorphic phenotype of this case might indicate that compound heterozygote mutation of the null allele and C-terminal and/or transmembrane mutations cause mild to moderate clinical phenotype because of significant residual enzyme activities.
We performed a muscle biopsy because of the patient’s sustained hypotonia and her motor developmental delay. Muscle pathology revealed small uniform fibers without specific structural abnormalities. Severe hypotonia is almost universal in Smith-Lemli-Opitz syndrome cases at infancy. Therefore, small muscle fibers, delayed muscle fiber growth, and a congenital muscle hypoplasia may contribute to the early hypotonia and motor delay of this syndrome, which may be partly central in origin.

Clinical diagnosis of Smith-Lemli-Opitz syndrome is difficult because many organs are affected, and the phenotypic presentation varies from lethal to mild. In addition, the incidence is very low in East Asians, so we are likely to miss the diagnosis of Smith-Lemli-Opitz syndrome in this population. Considering the wide spectrum of phenotypes, which varies from classic cases to mild mental retardation with inconclusive clinical findings, clinicians should implement a low threshold for biochemical testing of patients with developmental delays or hypotonia with dysmorphism.

In summary, our report is the first to describe a Korean patient with a typical presentation of Smith-Lemli-Opitz syndrome. The patient was a compound heterozygote of the null allele (1127delA) and an R352W missense mutation. Her parents each had 1 of the heterozygote mutations. Although the incidence of Smith-Lemli-Opitz syndrome is believed to be very low among Asians and Africans, a low level of awareness and recognition may partly be responsible for the apparently low incidence. Further efforts are needed to increase recognition of this syndrome among clinicians and to determine the frequency of carriers of mutations associated with Smith-Lemli-Opitz syndrome among Koreans.

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References


